

### **Remarks**

Applicants note with appreciation the telephonic interview granted by the Examiner and conducted on 21 October 2008. Accordingly, the independent claim 1 has been amended such that greater clarity is provided with respect to the feature that ***water is not being used as a solvent*** within the context of the present invention, which will be discussed in more detail hereinbelow.

Applicants further note with appreciation the withdrawal of rejections of claims 1, 10-11, 13-15, and 31-33 under 35 U.S.C. § 112, second paragraph, in light of Applicant's last filed amendment dated April 11, 2008.

By this paper, claim 1 has been amended; claim 2 is canceled; and claims 35-37 have been newly added. Support for the amendment is found, *inter alia*, in [0021], [0023], [0073], [0075] and [0086] of the published specification. No new matter is introduced by this amendment.

Claims 1, 4-15, 23 and 31-33 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kumar et al. (Tetrahedron letters, 1991, 32(16):1901-1904, hereinafter *Kumar*).

Currently, claims 1, 4-15, 23, 31-33 and 35-37 are pending in the application.

### **Remarks Directed To Rejections Of Claim 1, 4-15, 23 And 31-33 Under 35 U.S.C. § 102(b) Over Kumar**

Claims 1, 4-15, 23, and 31-33 stand rejected under 35 U.S.C. § 102(b) as being anticipated by *Kumar*. For at least the following reasons, Applicants respectfully traverse these rejections.

The final Office Action in relevant portion states:

*Kumar* relates to a new chemoenzymatic synthesis of optically pure (R)-Tomoxetine and both the enantiomer of fluoxetine (see abstract) ... The Examiner therefore believes that *Kumar* reads onto claims 1 and 14-15 because *Kumar* teaches the reduction of starting material which is a ketone into a final product which is alcohol, and thus the reaction must inherently have all of the features as claimed. . . .

*Kumar* teaches the reduction of ketone to an alcohol, as claimed. ***Since the starting material and the final product are made, it is inherent that the reference's method reaction was under the same reaction conditions as claimed.*** In regards to the argument that "it is clear that the water to yeast ratio of 6 ml/g is far greater than the ratio of up to 1.5 ml/g recited in claim 1", applicant is directed to the *Kumar* reference indicating that "Baker's yeast reduction of 3 yield ethyl 3-hydroxy-3-phenyl propionate (4) has been reported (by Deol) to five not more than 66% ee. Using modified conditions we have been able to obtain 4 in 85% ee" (see p. 1901, lines 4-6 of 3<sup>rd</sup> paragraph). Furthermore, *Kumar* (in the reference section), indicates that the value reported by Deol was later found to be 54 by Soai et al (see p. 1904, Reference 5). ***Since the reaction conditions (organic compound, yeast mediated reduction, water, final product) are at met, the reaction must inherently have all of water-to-yeast ratio, temperature conditions, pressure, and must be under the same conditions*** (i.e., all of reaction conditions including separation steps) ...

(pages 3-4 of the final Office Action with emphasis added).

The independent claim 1 in current form recites a method of reducing an organic compound, the method including subjecting the organic compound to a ***yeast-water paste*** of a yeast mediated reduction . . . wherein a water-to-yeast ratio is up to 1.5 ml/g" (emphasis added).

Yeast-water paste as recited in the independent claim 1 in current form is understood to mean that the water is ***not*** used as a solvent ([0017]). The water is present in such a small amount that it ***sticks*** to the yeast ([0023]), and as such the yeast mediated reduction is conducted in the ***absence of a solvent*** ([0050]). Moreover, the yeast-water paste can become a moist pliable yeast that gets firmed up a few minutes after water has been incorporated into the yeast ([0073]), and the yeast-water paste can be spreadable over a filter paper ([0075]).

*Kumar* and or *Deol* cross -referenced in *Kumar* fails to teach a yeast-mediated reduction using a yeast-water past recited in the independent claim 1. In fact, and as presented in Applicants' last filed amendment of April 11, 2008, *Kumar* with or without *Deol*, fails to even teach or suggest the limitation of "wherein a water-to-yeast ratio is up to 1.5 ml/g" further recited in the independent claim 1 and all the claims dependent therefrom. Please see:

The Examiner's attention is directed to reference five (5) incorporated on page 1901 of *Kumar* with the reference titled "Asymmetric Reduction of Carbonyl Compounds by yeast II preparation of optically active  $\alpha$ - and  $\beta$ -Hydroxy Carboxylic Acid Derivatives" to Deol et al. (hereinafter *Deol*).

The *Deol* describes, in detail, the "Baker's yeast reduction" mentioned at page 1901, 3<sup>rd</sup> paragraph of *Kumar*. In particular, *Deol* in relevant portion provides:

Method A.-- A thick suspension of industrial yeast (100g of wet-packed Fermex brand, Fermentation Industries, Granville, N.S.W.), sucrose (100g) in water (600ml) was prepared and kept at room temperature until vigorous gas production ensued (about 30 min). (Emphasis Added)  
*Deol*, page 2464

From the experimental section of *Deol* cited above, it is clear that "wet packed Fermex" yeast is added to 600ml water to form a thick suspension. One skilled in the art would readily observe a water phase out of a 600 ml water mixture containing only 100g of yeast. As such, the water to yeast ratio of 600ml/100g or 6 ml/g taught in *Kumar* as detailed in *Deol* is far greater than the ratio of up to 1.5 ml/g as recited in claim 1. This drastic difference is confirmed by the Examiner that "the specification of the instant application describes 10g of yeast with 10ml of water" which equates to a water to yeast ratio of 10ml/10g or 1ml/g, whereas *Kumar* through the incorporated *Deol* reference teaches the water to yeast ratio of 6ml/g – a value six times the specific ratio of 1ml/g referenced by the Examiner.

(pages 9-10 of Applicants' last filed amendment dated April 11, 2008)

The observation that *Kumar* uses yeast and water to illustratively produce Fluoxetine or Tomoxetine (page 1902) does not, without anything more, become inherently anticipatory of all conditions including water-to-yeast ratio.

MPEP 2112 in relevant portions provides:

IV. EXAMINER MUST PROVIDE RATION-ALE OR EVIDENCE TENDING TO SHOW INHERENCY

***The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert***, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Red. Cir. 1993) reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. ***Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficiency. In re Robertson***, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Circ. 1999).

Using a yeast-water paste to conduct yeast-mediated reduction of the organic compound wherein a water-to-yeast ratio is up to 1.5 ml/g, as recited in the independent claim 1 is ***no more than a mere probability or possibility***, nor is it necessarily present in *Kumar* from the above-described given circumstances in *Kumar* and or *Deol*, pursuant to MPEP 2112 cited above.

Furthermore, the criticality of the use of water in an amount so as to form the yeast-water paste according to the independent claim 1, is further demonstrated in the results shown in Exhibit 1. Exhibit 1, along with Exhibit 2 presented hereinbelow, shows trial experiments relating to one or more embodiments of the present invention conducted under the supervision of Dr. Andrew John Smallridge, one of the co-inventors of the present application. According to Exhibit 1, the pages numbered 19 and 20 provided therein depict reactions conducted with enol ethers in an organic solvent petroleum ether (PE) did not work, as indicated by the crosses placed next to the reaction formulas.

Therefore, the cited prior art fails to teach either expressly or inherently the aforementioned limitation of claim 1. Claim 1 and all the claims dependent therefrom are submitted to be patentable.

Reconsideration and withdrawal of the rejections to claims 1, 4-15, 23 and 31-33 under 35 U.S.C. 102(b) is solicited.

**Remarks Directed to Newly Added Claims 35-37**

Claims 35-37 are newly added. Support for the amendment is found, as stated hereinabove, in [0021], [0023], [0073], [0075], and [0086] of the published specification. These newly added claims are submitted to be patentable based on their respective dependency from the independent claim 1, now believed to have been allowable in light of the amendment and remarks stated above. Moreover, Applicants submit that independent ground exists as to the patentability of claims 36 and 37 as shown below.

**Re: claim 37**

Claim 37 recites the method according to claim 1, wherein the yeast mediated reduction is carried out in ***non-fermenting*** conditions.

As non-fermenting conditions ***involve no energy source*** and in particular no glucose or sucrose as in the case of the present invention embraced by the instant claim 37, *Kumar* clearly teaches rather to the contrary a fermenting process wherein yeast, glucose, and ample water are all required. Please see for instance the first line of text underneath the formulas on page 1902. Similarly, *Deol* as referenced in *Kumar* also teaches the reduction of ketone by actively *fermenting* yeast (Introduction) and in particular a fermenting reaction of yeast, *sucrose* in ample water (Discussion).

Exhibit 2, briefly mentioned above and submitted concurrently herewith, provides results of yeast mediated reduction of enol ethers conducted under the fermenting condition

employing sucrose and ample water pursuant to "Ridley" (co-author with B. S. Deol on the *Deol* reference).

Contrary to the relatively acceptable yield reported in [0080]-[0084] of the instant specification, reduction ethyl end ether in *Deol* or *Ridley's* fermenting condition was found not to be successful, in fact, there was "no reaction" observable.

As discussed above, neither *Kumar* nor *Deol* teaches or suggests the aforementioned limitation of non-fermenting conditions according to claim 37. Claim 37 is submitted to be patentable based on at least this independent ground, aside from its dependency from claim 1, which is now believed to have been allowable in light of the instant amendments and remarks stated hereinabove.

Re: Claim 36

Claim 36 recited the method of claim 1, wherein the method ***avoids biphasic extractions*** before the step of adding the organic solvent to the mixture (emphasis added).

At a time just prior to the present invention, the art was confronted with the obstacles associated with the yeast-catalyzed reactions utilizing aqueous solvent systems that were found inconvenient for large-scale extraction and purification ([0011] of the published specification). As large amounts of water used therein have to be extracted out via a so-called biphasic extraction, conventional yeast-mediated methods often involved many setbacks including unsatisfactory low optical yields or relatively low purity.

As directly contrary to these conventional methods, the method according to the instant claim 36 ensures that the water is used in an amount, for example mere enough to form a yeast-water paste, such that the water sticks to the yeast and does not interfere with the removal of the reaction product into an organic solvent. As such, it is a significant advantage of the method of claim 36 that a biphasic (aqueous/organic) extraction can be avoided ([0023] of the published specification).

*Kumar* or *Deol* fails to teach or suggest the aforementioned limitation as to the avoidance of biphasic extraction according to claim 36, claim 36 is submitted to be patentable at least on this independent ground, aside from its dependency from claim 1, which is now believed to have been allowable in light of the instant amendments and remarks stated hereinabove.

### **Conclusion**

Applicants submit that the claims are in conditions for allowance and respectfully request a notice to that effect. If the Examiner believes that a telephonic conference will advance the prosecution of this application, such a conference is invited at the convenience of the Examiner.

The Petition fee of \$245.00 is being charged to Deposit Account No. 02-3978 via electronic authorization submitted concurrently herewith. The Commissioner is hereby authorized to charge any additional fees or credit any overpayments as a result of the filing of this paper to Deposit Account No. 02-3978.

Respectfully submitted,

**Maurice Arthur Trewhella et al.**

By /Junqi Hang/

Junqi Hang  
Reg. No. 54,615  
Attorney for Applicant

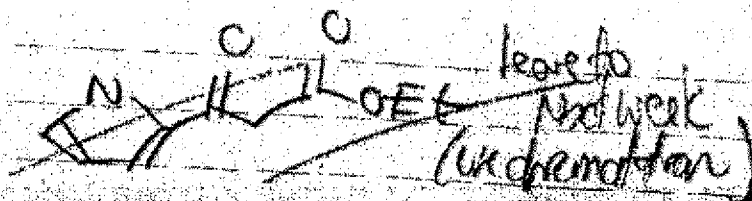
Date: December 9, 2008

**BROOKS KUSHMAN P.C.**  
1000 Town Center, 22nd Floor  
Southfield, MI 48075-1238  
Phone: 248-358-4400  
Fax: 248-358-3351

# **EXHIBIT 1**



making more



- need to go over water XM reaction (no better added)  
 (Do these reactions work with end ether?)

① ethyl ester (0.0173g) 1/8 mm  
 one  
 one OEt 8000/1000

② one (0.0166g) 1/8 mm  
 one OEt 8000/1000  
 one OEt 8000/1000

Ridley  
1975

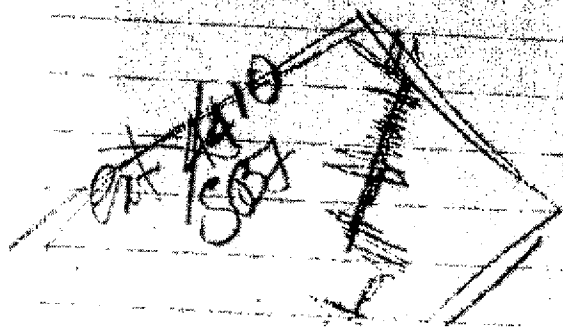
using conditions from Ridley paper

Arch

No reaction

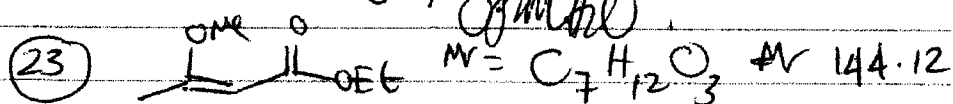
\* do CN ester reaction (try solvent)  
 \* place more NH<sub>2</sub> ester (to make more  
 this time) → need enough for 3 reactions  
 (0.05/0.05) PE/EA solvent for chem

VA need more eqn (can't work well) make more



## **EXHIBIT 2**

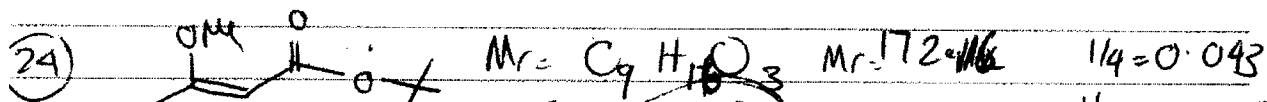
5g Y, PE (50)



$$1/4 = 0.03605$$

$$1/8 = 0.0180$$

- (A) 0.0178g x  
(B) 0.0177g  
(C) 0.0184g x

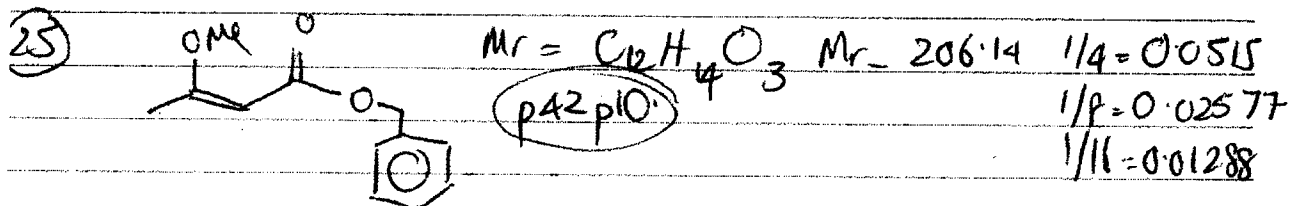


$$1/4 = 0.043$$

$$1/8 = 0.0215$$

$$1/16 = 0.01076$$

- (A) 0.0110g x  
(B) 0.0106g x  
(C) 0.0109g x

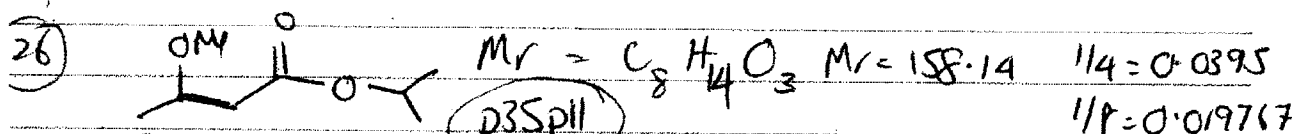


$$1/4 = 0.0515$$

$$1/8 = 0.02577$$

$$1/16 = 0.01288$$

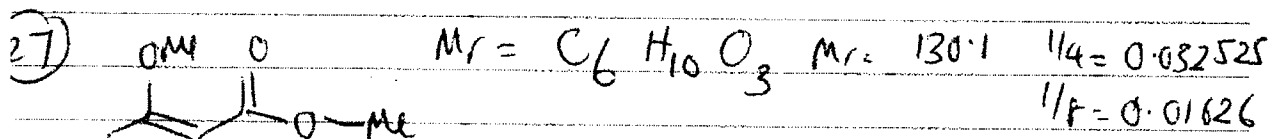
- (A) 0.0132g x  
(B) 0.0135g x  
(C)



$$1/4 = 0.0395$$

$$1/8 = 0.019767$$

- (A) 0.0202g x  
(B) 0.0202g x  
(C)

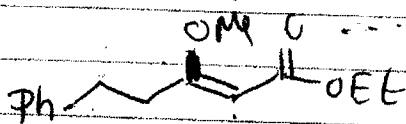


$$1/4 = 0.032525$$

$$1/8 = 0.01626$$

- (A)  
(B)  
(C)

(28)



$$M_r = C_{14}H_{18}O_3 = 234.18$$

p42p7

$$1/4 = 0.05855$$

$$1/8 = 0.02927$$

$$1/16 = 0.01464$$

(A) 0.0147g

(B) 0.0145g

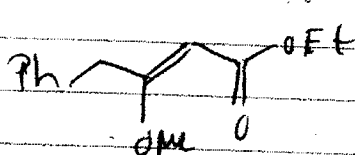
(C) 0.0146g

x

x (?)

x

(29)



$$M_r = C_{13}H_{16}O_3 = 220.16$$

p13p3

$$1/4 = 0.05504$$

$$1/8 = 0.02752$$

$$1/16 = 0.01376$$

(A) 0.0133g

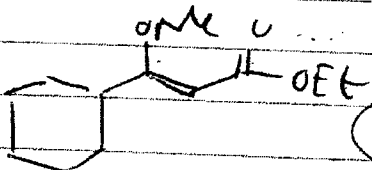
(B) 0.0138g

(C) 0.0137g

x

x

(30)



$$M_r = C_{12}H_{20}O_3 = 212.2$$

p13p4

$$1/4 = 0.05305$$

$$1/8 = 0.026525$$

$$1/16 = 0.01326$$

(A) 0.0131g

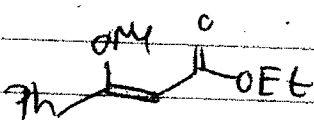
(B) 0.0134g

(C) 0.0133g

x

x

(31)



$$M_r = C_{12}H_{14}O_3 = 206.14$$

$$1/4 = 0.0515$$

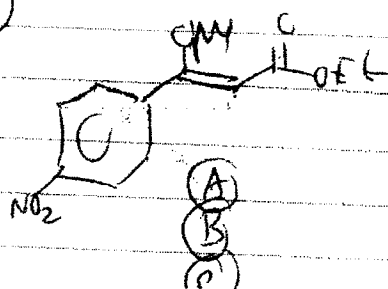
$$1/8 = 0.02577$$

(A)

(B)

(C)

(32)



$$M_r = C_{12}H_{13}O_5N = 251.13$$

$$1/4 = 0.06278$$

$$1/8 = 0.03139$$

(A)

(B)

(C)